Diphtheria

1. DISEASE REPORTING

A. Purposes of Reporting and Surveillance

1. To assist in the diagnosis of cases.
2. To assure early and appropriate treatment with diphtheria antitoxin and antibiotics.
3. To identify and evaluate contacts and recommend appropriate antibiotic prophylaxis and/or immunization to prevent further spread of the disease.
4. To alert public health authorities to the presence of diphtheria cases and the possibility of additional cases developing in the area, a particular concern given the large number of susceptible adults.

B. Legal Reporting Requirements

1. Health care providers: **immediately notifiable to local health jurisdiction.**
2. Hospitals: **immediately notifiable to local health jurisdiction.**
3. Laboratories: notifiable to local health jurisdiction within 2 work days, specimen submission required.
4. Local health jurisdiction: notifiable to the Washington State Department of Health (DOH) Communicable Disease Epidemiology Section (CDES) within 7 days of case investigation completion or summary information required within 21 days

C. Local Health Jurisdiction Investigation Responsibilities

1. Begin case investigation immediately. Please inform CDES about possible cases. CDES will assist with release of antitoxin if necessary.
2. Facilitate the transport of specimens to assist with the diagnosis.
3. Recommend measures to prevent further spread from the case.
4. Identify and evaluate contacts; educate and recommend measures to prevent further spread from contacts.
5. Report all *confirmed* and *probable* cases (see Section 3C) to CDES. Complete the diphtheria case report form (www.doh.wa.gov/notify/forms/diphtheria.doc) and enter the data into the Public Health Issues Management System (PHIMS).

2. THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic Agent

Diphtheria is caused by toxigenic strains of the bacteria *Corynebacterium diphtheriae*. Exotoxin production results when the bacteria are infected by a bacteriophage carrying the toxin-producing gene (tox gene). Only toxigenic strains can cause severe disease. *C. diphtheriae* has three biotypes: gravis, intermedius, and mitis. The gravis biotype is associated with the most severe disease, but any strain may produce toxin. ALL clinical

isolates of *C. diphtheriae* should be tested for toxigenicity. Nontoxigenic strains have been increasingly associated with infective endocarditis.

B. Description of Illness

Classic diphtheria is an upper-respiratory tract illness characterized by sore throat, low-grade fever, and an adherent pseudomembrane of the tonsil(s), pharynx, and/or nose. However, disease can involve almost any mucous membrane. For clinical purposes, diphtheria can be classified according to the site of the infection:

1. Anterior nasal diphtheria

Anterior nasal diphtheria usually presents with mucopurulent discharge from the nose which may be bloody and a white pseudomembrane on the nasal septum.

2. Pharyngeal and tonsillar diphtheria

Pharyngeal and tonsillar diphtheria, the most common type of infection, initially presents with malaise, sore throat, anorexia, and low-grade fever. Within a few days, a bluish-white pseudomembrane forms on one or both tonsils which can extend to the tonsillar pillars, uvula, soft palate, pharynx and nasopharynx. Over time, the pseudomembrane evolves into a dirty gray color with areas of green or black necrosis surrounded by a minimal amount of erythema. Attempts to remove the pseudomembrane cause bleeding. With severe disease, patients can develop edema of the anterior neck giving a characteristic "bullneck" appearance. If a significant amount of toxin is absorbed into the blood stream, patients may develop pallor, rapid pulse, coma and death.

The differential diagnosis of diphtheria includes streptococcal pharyngitis, viral pharyngitis, Vincent's angina, infectious mononucleosis, oral syphilis and candidiasis.

3. Laryngeal diphtheria

If the infection involves the larynx, the patient can present with fever, hoarseness and a barking cough.

4. Cutaneous (skin) diphtheria

Cutaneous diphtheria may present as a scaling rash or as clearly demarcated ulcers. Peripheral effects of the toxin are usually not evident. Since 1980, cutaneous diphtheria caused by either toxigenic or non-toxigenic strains of *C. diphtheriae* has not been reportable to the National Notifiable Disease Surveillance System (NNDSS) in the United States. Nevertheless, all *C. diphtheriae* isolates should be submitted for testing to determine whether the tox gene is present.

Other possible sites of infection include the conjunctiva, vulvovaginal area and external auditory canal. Complications of diphtheria include myocarditis, neuritis, airway obstruction, and death. The case-fatality rate for diphtheria is approximately 10%.

Rarely, other *Corynebacterium* species (*C. ulcerans* and *C. pseudotuberculosis*) may produce diphtheria toxin and cause classic respiratory diphtheria-like illness.

C. Diphtheria in the United States and Washington State

Diphtheria is rare in the United States with only 0–5 cases reported annually. The last major outbreak in the United States occurred in Seattle, Washington. There were three

outbreaks of cutaneous diphtheria in Seattle from 1972 through 1982. The first outbreak was due to a toxigenic strain while the later outbreaks were nontoxigenic strains. The last case of toxigenic diphtheria reported in Washington occurred in 1979. Cases now occur only rarely and are travel-associated since diphtheria is no longer endemic in Washington.

Between 1980 and 2005, 55 cases of diphtheria were reported in the United States. The majority of cases (77%) were in persons 15 years of age and older, and 4 of 5 fatal cases were in unvaccinated children. Although few cases of respiratory diphtheria have been reported in recent years, enhanced surveillance has shown ongoing circulation of toxigenic *C. diphtheriae* in a Northern Plains Indian community, where the disease was previously endemic, and in some communities in Canada. Cutaneous diphtheria due to nontoxigenic strains is still known to occur, particularly among homeless persons.

D. Reservoir

Infected humans are the reservoir.

E. Modes of Transmission

Diphtheria is transmitted from person to person through respiratory droplets or less commonly, through contact with discharge from skin lesions. Rarely, raw milk and fomites have served as vehicles.

F. Incubation Period

The incubation period is usually 2–5 days (range 1–10 days).

G. Period of Communicability

Persons are communicable for up to 4 days after treatment with effective antibiotics. Untreated persons generally shed bacteria from the respiratory tract or from skin lesions for 2–4 weeks after infection. A chronic carrier state is rare, but known to exist and such a carrier may shed organisms for 6 months or more.

H. Treatment

The mainstay of treatment for diphtheria is prompt administration of diphtheria antitoxin. If diphtheria is strongly suspected on the basis of clinical findings, antitoxin should be given immediately after specimens for bacteriologic testing are collected without waiting for results.

CDC stores diphtheria antitoxin (DAT) at quarantine stations around the country. DAT is currently available for treatment of respiratory diphtheria under an FDA-approved Investigational New Drug (IND) protocol. Since the antitoxin is of equine origin, a test to rule out hypersensitivity should be performed before administration.

Healthcare providers who suspect diphtheria should contact their local health department immediately. The local health jurisdiction in collaboration with DOH can assist with arranging consultation and transport of antitoxin as needed. For additional information regarding DAT, see: http://www.cdc.gov/vaccines/vpd-vac/diphtheria/dat/dat-main.htm

In addition to diphtheria antitoxin which is the primary therapy, patients should also be

treated with erythromycin or procaine penicillin G for 14 days to stop toxin production, eradicate *C. diphtheriae* and prevent further spread.

I. Immunity

Lifelong immunity is usually, but not always, acquired after disease or inapparent infection. Immunization with diphtheria toxoid produces prolonged but not lifelong immunity. Serosurveys in the United States indicate that more than 40% of adults lack protective levels of circulating antitoxin. However, many of these older adults may have immunologic memory and would have some protection against disease if exposed.

3. CASE AND CONTACT DEFINITIONS

A. Clinical description

Classic diphtheria is an upper-respiratory tract illness characterized by sore throat, low-grade fever, and an adherent pseudomembrane on the tonsil(s), pharynx, and/or nose. However, disease can involve almost any mucous membrane. For clinical purposes it is convenient to classify diphtheria into a number of manifestations depending on the site of disease:

- anterior nasal diphtheria
- pharyngeal and tonsillar diphtheria
- laryngeal diphtheria
- cutaneous (skin) diphtheria

B. Laboratory criteria for diagnosis

- Isolation of *Corynebacterium diphtheriae* from a clinical specimen, or
- Histopathologic diagnosis of diphtheria

C. Case classification (1995)

1. *Probable*: a clinically compatible case that is not laboratory confirmed and is not epidemiologically linked to a laboratory-confirmed case
2. *Confirmed*: a clinically compatible case that is either laboratory confirmed or epidemiologically linked to a laboratory-confirmed case

D. Comment

Respiratory disease caused by nontoxigenic *C. diphtheriae* should be reported as diphtheria. All *C. diphtheriae* isolates, regardless of association with disease, should be submitted to the State Public Health Laboratories and will be sent to the Diphtheria Laboratory, National Center for Infectious Diseases, CDC.

4. DIAGNOSIS AND LABORATORY SERVICES

A. Diagnosis

The initial diagnosis of diphtheria is usually based on the clinical presentation since it is imperative to begin presumptive therapy quickly.

Culture and toxigenicity testing: Diphtheria is confirmed by isolation of *Corynebacterium diphtheriae* on culture and toxigenicity testing. Health care providers who suspect diphtheria need to alert their laboratory that diphtheria is suspected. Culture medium containing tellurite is preferred because it provides a selective advantage for the growth of *C. diphtheriae.* However, since tellurite medium is not readily available in most laboratories, a blood agar plate can also be inoculated. If diphtheria bacilli are isolated they MUST be tested for the presence of the toxin-producing gene. A PCR assay is now available for testing *C. diphtheriae* isolates for the presence of the toxin-producing gene at PHL.

If the patient received antibiotics prior to specimen collection and the patient is receiving DAT, a clinical specimen can be tested directly for the presence of the tox gene at CDC using PCR.

Serologic testing: Serum collected prior to the administration of DAT can assist with assessing the probability of the diagnosis. This may be especially helpful if antibiotics were administered prior to collection of specimens for culture. Persons with serum antibody levels less than 0.01 IU/ml are likely to be susceptible to diphtheria while levels between 0.01–0.09 IU/ml indicate basic immunity. Testing for levels of immunity is available at commercial laboratories.

B. Tests Available at DOH Public Health Laboratories (PHL)

PHL can culture clinical specimens for *C. diphtheriae*. PHL can also perform PCR on *C. diphtheriae* isolates to detect the presence of the toxin-producing gene. All *C. diphtheriae* isolates will be forwarded to CDC. If the patient is receiving DAT, CDC will perform additional toxigenicity testing (i.e., ELEK test) to verify toxin expression.

PHL and CDC do not perform serologic testing for diphtheria.

All requests for diphtheria testing to be done at PHL must have approval from a Communicable Disease Epidemiology Section epidemiologist.

C. Specimen Collection

Culture specimens: Using respiratory precautions, health care providers should collect specimens from both the throat and nasopharyngeal area including the area underneath the edge of the pseudomembrane if possible. Collection of a portion of the adherent pseudomembrane in addition to the swabs is ideal. Throat cultures should be obtained with a cotton or Dacron® swab and placed in Amies or similar transport media. Clinical specimens should reach the PHL as quickly as possible after collection.

If the patient received antibiotics prior to specimen collection and the patient is receiving DAT, a clinical specimen can be tested directly for the presence of the tox gene at CDC using PCR. Respiratory specimens for PCR testing should be collected using a Dacron® swab and placed in a dry sterile container at 4° C.

Suspected diphtheria isolates and clinical specimens should be submitted with a completed DOH microbiology form available at:
http://www.doh.wa.gov/EHSPHL/PHL/Forms/Microbiology.pdf

For additional information regarding laboratory testing for diphtheria, see:
http://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.pdf

5. ROUTINE CASE INVESTIGATION

Interview the case and/or others who might be able to provide pertinent information.

A. Evaluate the Diagnosis

Review the clinical presentation, risk factors for exposure, and immunization status to determine the likelihood of the diagnosis. Immediately consult with Communicable Disease Epidemiology Section staff.

If diphtheria is highly suspected, do the following:

- Assure that the patient is in respiratory isolation with droplet precautions.
- Request that specimens are collected to confirm the diagnosis. Facilitate the transportation of specimens to the Public Health Laboratories.
- Collect serum to be held for serologic testing, as needed.
- Consult with CDES and CDC regarding the need for treatment with diphtheria antitoxin. Recommend the initiation of antibiotic treatment. Treatment should not be delayed pending laboratory confirmation when the diagnosis of diphtheria is strongly suspected.

If the suspicion of diphtheria is low, specimens can be sent to a commercial laboratory, but the laboratory staff should be alerted that diphtheria is included in the differential diagnosis.

B. Identify Source of Infection

Ask the patient about potential sources of infection in the 10 days prior to onset including:

- Travel out of the country, especially to an area where diphtheria is still endemic;
- Contact with persons from a country where diphtheria is still endemic; and
- Working or volunteering in a health care setting.

The search for carriers by use of nose and throat cultures, other than among close contacts, is not ordinarily useful or indicated.

C. Identify Close Contacts

Identify all close contacts, particularly household members and others who were directly exposed to respiratory secretions of the case, and determine their immunization status. See below for managing contacts.

D. Environmental evaluation

None

6. CONTROLLING FURTHER SPREAD

A. Infection Control Recommendations / Case Management

1. Hospitalized patients with pharyngeal diphtheria should be cared for using droplet precautions until they are off antimicrobial therapy and two cultures taken at least 24

hours apart, and at least 24 hours after cessation of antimicrobial therapy, fail to show diphtheria organisms.

2. Hospitalized patients with cutaneous diphtheria should be cared for using contact precautions until they are off antimicrobial therapy and two cultures taken at least 24 hours apart, and at least 24 hours after cessation of antimicrobial therapy, fail to show diphtheria organisms.
3. Persons with diphtheria should avoid close contact with others until two cultures taken 24 hours apart, and at least 24 hours after cessation of antimicrobial therapy, fail to show diphtheria organisms.
4. All articles soiled by respiratory or cutaneous discharges of a patient with diphtheria should be cleaned using contact precautions.
5. Persons with diphtheria should be vaccinated with diphtheria toxoid during convalescence since clinical disease does not necessarily confer immunity.

B. Contact Management

1. Close contacts with symptoms compatible with diphtheria should be referred to a health care provider immediately.
2. Close contacts should have cultures taken from the nose and throat, regardless of their immunization status or the presence of symptoms.
3. After collecting cultures, close contacts should receive a single dose of benzathine penicillin (IM) (600,000 units for persons less than 6 years of age and 1.2 million units for persons 6 years of age or older) or a 7–10 day course of oral erythromycin (40 mg/kg/d for children and 1 g/d for adults), regardless of their immunization status. Contacts who are found to have positive cultures should have cultures repeated after completion of therapy to ensure that eradication of the organism has occurred.
4. Previously immunized close contacts should receive a booster dose of diphtheria toxoid if more than 5 years have elapsed since their last dose. Unimmunized contacts should initiate the primary series immediately.
5. Close contacts should watch for symptoms of diphtheria during the 7–10 days after exposure, particularly if they are unimmunized.
6. Close contacts who handle food or work with school children should be excluded from work or school until bacteriologic examination proves them not to be carriers. (Transmission of diphtheria through raw milk has been documented.)

   For additional information regarding case investigations, see the CDC VPD Surveillance Manual available at: http://www.cdc.gov/vaccines/pubs/surv-manual/chpt01-dip.htm

C. Environmental measures

None

7. MANAGING SPECIAL SITUATIONS

Special situations will be handled on a case by case basis. Consult with Communicable Disease Epidemiology Section.

8. ROUTINE PREVENTION

A. Immunization Recommendations

Routine immunization with diphtheria toxoid in combination with tetanus toxoid and acellular pertussis vaccine as DTaP is recommended for all children younger than 7 years of age according to the schedule below (Table). If a child has a contraindication to the pertussis vaccine, pediatric DT should be used to complete the childhood vaccination series.

Table: Routine Childhood DTaP Vaccination Schedule

Dose	Age	Minimal Interval
Primary 1	2 months	N/A
Primary 2	4 months	4 weeks
Primary 3	6 months	4 weeks
Primary 4	15–18 months	6 months
Booster*	4–6 years	

* The booster dose for children is not required if the fourth dose is given on or after the fourth birthday

In addition to the primary series given in childhood, booster doses of diphtheria toxoid are recommended every 10 years. The first booster dose may be given at 11–12 years if at least 5 years have passed since the last dose of DTaP or DT. The ACIP recommends that this dose be given as Tdap followed by Td every 10 years. All adults < 65 years of age should receive a one-time dose of Tdap instead of the next scheduled Td for booster immunization against tetanus, diphtheria and pertussis.

For additional information regarding use of the tetanus vaccines, adverse reactions and contraindications see the most recent Red Book and Pink Book.

B. Prevention Recommendations

Immunization is the best way to prevent diphtheria.

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